

Claims

1. An injectable ultrasound contrast medium comprising  
5 biocompatible at body temperature gaseous substances which when in  
suspension in an aqueous carrier liquid containing usual surfactants,  
additives and stabilisers provide contrast agents for ultrasound echography,  
characterised in that the medium is a mixture of gases (A) and (B) in which,  
10 at least one of the gases (B), present in an amount of between 0.5 - 41% by  
vol., has a molecular weight greater than 80 daltons and its  
solubility in water is below 0.0283 ml of gas per ml of water measured under  
standard conditions, the balance of the mixture being gas A.
2. The ultrasound contrast medium of claim 1, wherein gas (B) is a  
15 fluorine-containing biocompatible gas.
3. The ultrasound contrast medium of claim 2, wherein the fluorine-  
containing gas is selected from the group consisting of SF<sub>6</sub>, CF<sub>4</sub>, C<sub>2</sub>F<sub>6</sub>, C<sub>2</sub>F<sub>8</sub>,  
C<sub>3</sub>F<sub>6</sub>, C<sub>3</sub>F<sub>8</sub>, C<sub>4</sub>F<sub>6</sub>, C<sub>4</sub>F<sub>8</sub>, C<sub>4</sub>F<sub>10</sub>, C<sub>5</sub>F<sub>10</sub>, C<sub>5</sub>F<sub>12</sub> and mixtures thereof.
- 20 4. The ultrasound contrast medium of claim 3, wherein the fluorine-  
containing gas is sulfur hexafluoride or octafluoro cyclobutane.
5. The ultrasound contrast medium of claim 1, wherein gas A is  
25 selected from the group consisting of air, oxygen, nitrogen, carbon dioxide  
and mixtures thereof.
6. An injectable ultrasound contrast agent comprising of a suspension  
30 of gas filled microbubbles or microballoons in a physiologically acceptable  
aqueous carrier comprising usual surfactants, additives and stabilisers,  
characterised in that the gas is a gas mixture of at least two biocompatible  
gases A and B in which at least one gas (B) present in an amount of between  
0.5 - 41% by vol. has a molecular weight greater than 80 daltons and solubility  
in water below 0.0283 ml per ml of water at standard conditions, the balance  
35 of the mixture being gas A.
7. The ultrasound contrast agent of claim 6, wherein gas (B) is a  
fluorine-containing biocompatible gas.

8. The ultrasound contrast agent of claim 7, wherein the fluorine-containing gas is selected from the group consisting of SF<sub>6</sub>, CF<sub>4</sub>, C<sub>2</sub>F<sub>6</sub>, C<sub>2</sub>F<sub>8</sub>, C<sub>3</sub>F<sub>6</sub>, C<sub>3</sub>F<sub>8</sub>, C<sub>4</sub>F<sub>6</sub>, C<sub>4</sub>F<sub>8</sub>, C<sub>4</sub>F<sub>10</sub>, C<sub>5</sub>F<sub>10</sub>, C<sub>5</sub>F<sub>12</sub> and mixtures thereof.

9. The ultrasound contrast agent of claim 6 or 7, wherein gas A is selected from the group consisting of air, oxygen, nitrogen, carbon dioxide or mixtures thereof.

10. The ultrasound contrast agent of claim 6, wherein the surfactants comprise at least one film forming surfactant present in laminar and/or lamellar form and, optionally, hydrophilic stabilizers.

11. The ultrasound contrast agent of claim 10, wherein the film forming surfactant is a phospholipid.

12. The ultrasound contrast agent of claim 11, wherein the phospholipid is selected from the group consisting of phosphatidic acid, phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylglycerol, phosphatidylinositol, cardiolipin, sphingomyelin and mixtures thereof.

13. The ultrasound contrast agent of claim 11, wherein in addition to the phospholipid the aqueous carrier comprises copolymers of polyoxyethylene and polyoxypropylene, and glycerol.

14. The ultrasound contrast agent of claim 6, wherein the surfactants are soy bean oil, Tween® and/or sorbitol.

15. A dry formulation comprising surfactants, additives and stabilisers stored under a mixture of substances which at the body temperature are biocompatible gases, at least one of which is a gas whose molecular weight is greater than 80 daltons, and whose solubility in water is below 0.0283 ml per ml of water at standard conditions.

16. The dry formulation of claim 15, wherein the gas is fluorine-containing biocompatible gas.

17. The dry formulation of claim 16, wherein the fluorine-containing gas is present in the mixture in an amount between 0.5 - 41% by vol., the balance 59 - 99.5% by vol. being air, oxygen, nitrogen, carbon dioxide or mixtures thereof.

18. A two component kit comprising, as the first component, a dry formulation of surfactants, additives and stabilisers stored under a mixture of substances which at body temperature are gases and, as the second component a physiologically acceptable carrier liquid which, when admixed with the first component, provides, as a suspension of the two components, an ultrasound contrast agent, characterised in that at least one of the gases in the mixture is a gas whose molecular weight is greater than 80 daltons and whose solubility in water is below 0.0283 ml of gas per ml of water at standard conditions.

19. The two component kit of claim 18, wherein the gas is fluorine-containing biocompatible gas present in the mixture in an amount of between 0.5 - 41% by vol., the balance being air, oxygen, nitrogen, carbon dioxide or mixtures thereof.

20. The two component kit of claim 18 or 19, wherein the fluorine-containing gas is selected from the group consisting of SF<sub>6</sub>, CF<sub>4</sub>, C<sub>2</sub>F<sub>6</sub>, C<sub>2</sub>F<sub>8</sub>, C<sub>3</sub>F<sub>6</sub>, C<sub>3</sub>F<sub>8</sub>, C<sub>4</sub>F<sub>6</sub>, C<sub>4</sub>F<sub>8</sub>, C<sub>4</sub>F<sub>10</sub>, C<sub>5</sub>F<sub>10</sub>, C<sub>5</sub>F<sub>12</sub> and mixtures thereof.

21. A method of making the ultrasound contrast agent of claim 6, in which a gas mixture of at least two biocompatible components (A and B) is suspended in a physiologically acceptable aqueous carrier liquid containing usual surfactants, additives and stabilisers so as to form, gas filled microbubbles or microballoons, characterised in that the minimum effective proportion of at least one gas component in said mixture of gases is determined according to the criteria

$$B_c\% = K/e^b M_{wt} + C$$

in which B<sub>c</sub>% (by vol.) is the total quantity of the component B in the mixture, K, C and b are constants with values of 140, -10.8 and 0.012 respectively, M<sub>wt</sub> represents the molecular weight of the component B which is > 80.

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24. Use of the ultrasound contrast medium of claim 1 for the manufacture of ultrasound contrast agents.

del #1

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